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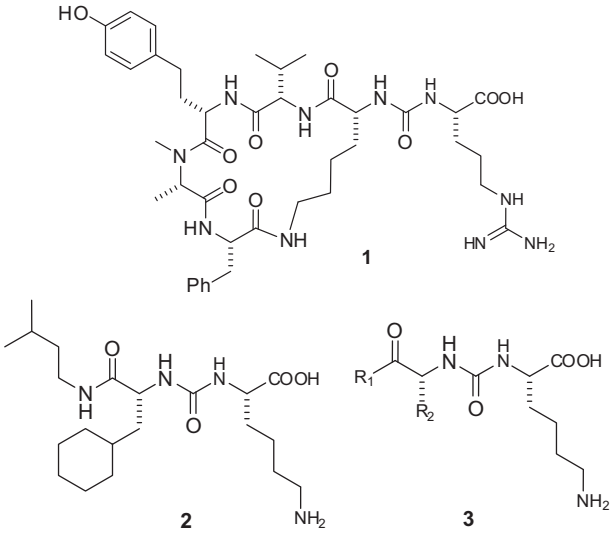
1. Current literature highlights

1.1. A library of small molecule inhibitors of activated thrombin activatable fibrinolysis inhibitor (TAFIa)

Efforts to find drugs that prevent inappropriate blood coagulation have generally focused on inhibition of thrombin, factor Xa (FXa) or factor VIIa (FVIIa). Other enzymes in the coagulation cascade have received considerably less attention. In particular TAFIa inhibition has no direct effect on coagulation or platelet function and yet is expected to present a novel antithrombotic mechanism with a low risk of bleeding.

TAFI is a 423 amino acid protein that is activated by thrombin by conversion to TAFIa. In this form it is capable of cleaving arginine and lysine residues from the surface of fibrin which results in reduced plasmin formation, protecting fibrin clots from degradation. A recent publication describes the discovery of naturally occurring macrocyclic TAFIa inhibitors, and their modification through library synthesis to generate novel and potent low molecular weight inhibitors [1].

Compounds isolated from an extract of the cyanobacteria, *Planktothrix rubescens*, were found to be macrocyclic peptidic inhibitors of TAFIa. One of these compounds, anabaenopeptin B (**1**), is an inhibitor of TAFIa with an IC_{50} value of 1.5 nM, and more than 500-fold selectivity over carboxypeptidases A and N, FXa, FVIIa, FIIa, and FXIa. In order to find smaller and simplified analogues for this macrocycle, and because TAFIa is unstable, an X-ray co-crystal structure was obtained of **1** bound to the related peptidase, carboxypeptidase B. From this structure, it was apparent that the polar groups, C-terminal arginine, the carboxylic acid and the urea were making key hydrogen-bonding interactions.



Following this observation, a number of smaller linear analogues were designed, prepared and tested against TAFIa. In particular, it was found that a compound such as **2**, although a thousand-fold less active as an inhibitor, was much lower in MW and in fact had a superior ligand efficiency value (LE = 0.27 kcal/mol, c.f. with 0.19 kcal/mol for compound **1**). To improve potency, a library of compounds (**3**) was made in which structural variation around the R_1 and R_2 positions was explored.

The best compounds discovered from this library had bulky lipophilic amines in the R1 position, such adamantane, norbornyl or bornyl derivatives. In particular, the (*R*)-(+)-bornylamide (**4**) was found to be a 3 nM TAFIa inhibitor. Variation of the R_2 substituent revealed a preference for a β-branched residue such as a cycloalkyl methylene, and cyclohexyl methylene remained the best group in the R_2 position.

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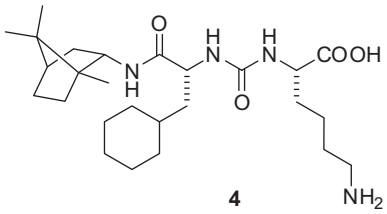

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Compound **4** was selected for further investigation, and was found to be reasonably stable in the presence of human, mouse or rat microsomes and human hepatocytes. The compound was also found to be highly selective for TAFIa over a panel of other proteases. The compound has displayed a promising *in vitro* profile and is a suitable candidate for progression to *in vivo* studies.

2. A summary of the papers in this month's issue

2.1. Polymer supported synthesis

A general synthesis of *N*-terminal aziridinyl-2-carbonyl (Azy) peptides has been developed aided by the photolabile *o*-nitrophenylethyl protecting group. This method enables the synthesis of unprotected Azy-terminated peptides incorporating ionisable groups using solid phase techniques followed by photorelease of the free *N*-terminal Azy moiety. The resulting Azy peptides undergo Cu(II)-mediated ligation with thioacids to give Azy-embedded peptides, providing a handle for site-specific modification of the peptide [2].

2.2. Solution-phase synthesis

The imidazolin-1-yl azine moiety, constructed using a recently developed Buchwald–Hartwig-type arylation methodology, displays excellent chemical stability under subsequent microwave-assisted Pd-catalysed amination with a range of *N*-nucleophiles. This finding has permitted the usage of imidazolin-1-yl azines for bioactive compound library design leading to the discovery of micromolar kinase inhibitors [3].

A general, sequential and efficient one-pot synthesis of natural product inspired chromeno[3,4-b]pyrrol-4(3*H*)-ones has been described. The one-pot reaction sequence consists of *N*-Boc deprotection of an *N*-substituted Boc-glycine *O*-aryl ester embodying an *ortho*-alkyne substituent, azomethine ylide generation with an aldehyde, subsequent intramolecular 1,3-dipolar cycloaddition with the alkyne followed by oxidative aromatisation. This method gives efficient access to a collection of highly substituted diverse pyrrolocoumarines [4].

Debromokeramadine has been isolated from the Pacific sponge *Agelas cf. mauritiana*, and described in a recent publication. The synthesis of debromokeramadine and its brominated analogue, keramadine, are described. This flexible approach was applied to the preparation of three debromo-analogues by varying the substitution of the guanidine bis-nucleophile. The reaction has been employed for the regio- and stereoselective synthesis of debromokeramadine analogues and a library of pyrrole-2-aminoimidazoles thereby allowing biological activity studies [5].

A two-step sequence involving an Ugi reaction followed by reductive Heck cyclisation has been evaluated in order to provide access to a 3-benzazepine framework in a diversity-oriented fashion. Several aspects related to the substrate scope and the optimal distribution of the required functional groups have been addressed, resulting in the construction of a small library of the title compounds, featuring four distinct types of substitution pattern [6].

A simple, cheap, efficient, and metal-free method for one-step synthesis of a library of 1,3-diheteroatom five-membered heterocycles with exocyclic CN and CC double bonds has been described. The convenient reaction proceeds via the direct three-component halocyclisation of propargylamines, heterocumulenes and I_2 [7].

Molecular libraries of natural product-like and structurally diverse compounds are attractive for early drug discovery campaigns. The synthetic methodology for library production of hexahydropyrrolo[2,1-*a*]isoquinoline (HPIQ) compounds has been presented. Two advanced HPIQ intermediates, both incorporating two handles for diversification, were synthesised through an oxidative cleavage/Pictet–Spengler reaction sequence in high overall yields. A subsequent metal-catalysed cross coupling/amidation protocol has been developed and its utility in library synthesis validated by construction of a 20-membered natural product-like molecular library in good overall yields [8].

An efficient synthetic approach to two amino-oxazoline compound libraries has been developed employing a branching cascade approach. Chromonylidene β-ketoester was a common precursor transformed into two different ring-systems: the pyridine and the benzopyrane substituted hydroxyphenones. In subsequent steps, the ketone moiety in two ring-systems was transformed into an amino-oxazoline ring, and the functional groups on the two amino-oxazoline scaffolds exploited further to generate a compound collection of around 600 amino-oxazolines [9].

A natural product-inspired synthesis of a compound collection embodying the tetrahydroindolo[2,3-*a*]quinolizine scaffold has been established with a five step synthesis route. An imino-Diels–Alder reaction between Danishefsky's diene and the iminoesters derived from tryptamines was used as a key reaction. Reductive amination of the ketone function and amide synthesis with the carboxylic acid derived from the ethyl ester, were used to decorate the core scaffold. In this way, a compound library of 530 tetrahydroindolo[2,3-*a*]quinolizines was generated and submitted to the European Lead Factory consortium for various biological assays [10].

The design, synthesis and decoration of six small molecule libraries has been described wherein each library was inspired by structures embedded in alkaloid natural product frameworks. The synthetic approaches required key steps including Pd-catalysed aminoarylation and dipolar cycloadditions. Libraries were subsequently nominated for production on the basis of the scope and limitations of the validation work, and the research led to the successful synthesis of >2500 novel alkaloid-like compounds for addition to the screening collection of the European Lead Factory [11].

Functionalised azepane and oxepane scaffolds have been prepared using diazocarbonyl chemistry and elaborated to show their potential use for library synthesis. Key dicarbonyl containing seven-membered rings were functionalised *via* diastereoselective Luche reduction of the ketone followed by manipulation of the ester and amine groups. Further scaffolds could be accessed by *C*-alkylation of the dicarbonyl compounds [12].

Scaffolds of natural products represent promising starting points for the development of focused compound libraries. The development of a synthetic route to a compound library based on the hexahydropyrrolo indole (HPI) scaffold has been described. A two-step approach consisting of a batch synthesis of an advanced functionalisable HPI intermediate followed by the establishment of reaction conditions that allow derivatisation of this scaffold at three different positions has been described, and the optimised methods were applied to the synthesis of a 276-member library [13].

Biologically relevant 6-aza-8-oxa[3.2.1]bicyclooctane scaffolds have been synthesised in a five-step procedure starting from furfural. In addition to showing that these scaffolds are amenable to decoration *via* standard functional group interconversions, further functionalisation *via* Lewis acid-mediated *N,O*-acetal opening, followed by nucleophilic trapping of the resulting intermediate cation has also been described. By using different nucleophiles, a modest library of 2,6-*trans*-disubstituted pyrans has been prepared in good yields and in a highly diastereoselective manner [14].

Work towards the development of a new strategy for the synthesis of rare and biologically interesting indolizin-5(3*H*)-ones, based around the use of ring-closing metathesis to construct the carbocyclic ring system, has been described. The study provided insights into the general stability of indolizin-5(3*H*)-ones and their tendency to exist as the tautomeric indolizin-5-ols, and approach has allowed access to other novel structurally related compounds based around unusual 6,5-azabicyclic scaffolds [15].

The application of a tandem condensation/cyclisation/[3+2]-cycloaddition/elimination reaction has given an sp^3-rich tricyclic pyrazoline scaffold with two ethyl esters, in a single step from a simple linear starting material. The successive hydrolysis and cyclisation (with Boc anhydride) of these 3-dimensional architectures, generated unprecedented 16-membered macrocyclic bisanhydrides. Selective amidations could then be achieved by ring opening with a primary amine followed by HATU-promoted amide coupling to yield an sp^3-rich natural product-like library [16].

2.3. Scaffolds and synthons for combinatorial libraries

The application of [4+2] cycloadditions between alkenes and an *N*-benzoyl iminium species, generated *in situ* under acidic conditions, has been described in the synthesis of diverse molecular scaffolds. The key reaction led to the formation of cyclic imidates in good yield and with high regioselectivity. It was demonstrated that the cyclic imidates may be readily converted into 1,3-amino alcohols. Incorporation of orthogonally-reactive functionality, such as aryl and alkyl bromides, into the cycloaddition substrates enabled the synthesis of additional scaffolds. For one scaffold, the synthesis of exemplar screening compounds was undertaken to demonstrate potential value in small molecule library production [17].

Scaffold diversity is key for the discovery of novel bioactive compounds using high throughput screening. Based on the Ugi tetrazole synthesis, novel bi- and tri-cyclic scaffolds featuring interesting pharmacophore properties have been designed. The compounds of the scaffold were synthesisable in large numbers and diversity in two steps using (hetero)phenylethylamines, HN_3, oxo components and iscyanoacetaldehyde(dimethylacetal). The chemistry is amenable to parallel synthesis and was used to enhance and fill the screening decks of the European Lead Factory. The recent publication reports full experimental details, scope and limitations of the reaction, cheminformatic analysis and the 3D structures of selected compounds [18].

A concise and efficient synthesis of cyclopentitols as a scaffold for a two-dimensional compound library for drug discovery has been described. Starting from D-mannose, the key steps were Wittig olefination and ring-closing metathesis (RCM) followed by a [3,3]-sigmatropic Overmann rearrangement to form an sp^3-rich, natural product-like scaffold from which a focused compound library with different functionalities was prepared [19].

A three component one-pot cascade reaction has been developed for the synthesis of 1,4,5-trisubstituted γ-lactams. The resulting scaffold can be modified independently at three positions, two of which are conveniently accessed by changing the components of the one-pot reaction. The phases of building block generation, scaffold synthesis and subsequent appendage modification were adapted to library production, resulting in a screening library of 500 compounds [20].

2.4. Solid-phase supported reagents

A simple, highly efficient and environmentally benign method for the synthesis of quinoxalines has been developed using a green and recyclable catalyst Amberlite IR-120H resin under solvent-free conditions. The catalyst can be recovered after completion of the reaction and can be reused as the catalytic property of the resin is not affected even up to four cycles [21].

Silica gel has been shown to readily adsorb strong Brønsted acids such as bis(trifluoromethanesulfonyl) imide to afford a heterogeneous supported catalyst that enables various acid-promoted reactions. The catalyst was recovered by means of easy filtration and reused for three successive runs. In addition, various acid-promoted reactions proceed smoothly with the reaction column system packed within silica gel-supported Brønsted acid [22].

2.5. Novel resins, linkers and techniques

An optimised, easy to scale-up synthetic route for a tetrahydrothiophene linker useful for the preparation of *C*-terminal peptide α-ketoacids has been recently described. Loading this linker on the solid support allows preparation of side-chain unprotected peptide cyanosulfurylides, which are easily oxidised to generate the corresponding *C*-terminal peptide α-ketoacids. The peptide α-ketoacids serve as protease inhibitors as well as segments for protein synthesis with the α-ketoacid–hydroxylamine amide-forming ligation [23].

The introduction of silicon in biologically-relevant molecules represents an interesting medicinal chemistry tactic. As part of the European Lead Factory efforts to generate novel, drug discovery-relevant chemical matter, the design and synthesis of 1,1-disubstituted-1-silacycloalkane-based compound libraries has been described [24].

2.6. Library applications

Synthetic strategies towards a library of amphiphilic tetraphenyl porphyrins anchored to synthetic saccharides and lipid modalities have been described. The carbohydrates and lipid functionalities are covalently linked to the model photosensitiser *via* a copper (I) catalysed alkyne azide cycloaddition reaction or an oxypropyl linkage achieved by nucleophilic substitution chemistry. Varying carbohydrate and lipid substituents allows for potential fine tuning of solubility and photophysical characteristics which are important for imaging and treatment applications in photomedicine, such as photodynamic therapy [25].

The leishmanicidal activities of a library of 2,6,9-trisubstituted purines that were screened for interaction with Cdc2-related protein kinase 3 (CRK3) and subsequently for activity against parasitic *Leishmania* species have been recently described. The most active compound inhibited recombinant CRK3 with an IC_{50} value of 162 nM and was active against *Leishmania major* and *Leishmania donovani* at low micromolar concentrations *in vitro* [26].

A comprehensive investigation of chemical constituents from brown algae *Stoechospermum marginatum* yielded ten known spatane compounds. To develop compound libraries based on these scaffolds, a series of semi synthetic derivatives was prepared and investigated for their antimicrobial and anticancer activities. The results indicated that several compounds exhibited potent cytotoxic activities against the B16F10 cancer cell line. Other analogues possessed potent antimicrobial activities against tested bacterial and fungal strains [27].

References

[1] Halland N, Brönstrup M, Czech J, Czechtizky W, Evers A, Follmann M, et al. Novel small molecule inhibitors of activated thrombin activatable fibrinolysis inhibitor (TAFIa) from natural product anabaenopeptin. J Med Chem 2015;58(11): 4839–44.

[2] Murray C, Dyer FB, Garner P. Solid phase synthesis and ligative processing of photocaged aziridine-2-carbonyl-terminated peptides. Tetrahedron Lett 2015;56(23):3636–8.

[3] Mujumdar P, Sarnpitak P, Shetnev A, Dorogov M, Krasavin M. Facile Pd-catalyzed amination of imidazolin-1-yl chloroazines under microwave irradiation: toward a new kinase-inhibitory chemotype. Tetrahedron Lett 2015;56(21):2827–31.

[4] Vidadala SR, Waldmann H. One-pot synthesis of a natural product inspired pyrrolocoumarine compound collection by means of an intramolecular 1,3-dipolar cycloaddition as key step. Tetrahedron Lett 2015;56(23):3358–60.

[5] Schroif-Grégoire C, Appenzeller J, Debitus C, Zaparucha A, Al-Mourabit A. Debromokeramadine from the marine sponge Agelas cf. mauritiana: isolation and short regioselective and flexible synthesis. Tetrahedron 2015;71(22): 3609–13.

[6] Peshkov AA, Peshkov VA, Pereshivko OP, Van der Eycken EV. Diversification of the 3-benzazepine scaold applying Ugi/reductive Heck sequence. Tetrahedron 2015;71(23):3863–71.

[7] Huang S, Shao Y, Liu R, Zhou X. Facile access to oxazolidin-2-imine, thiazolidin-2-imine and imidazolidin-2-imine derivatives bearing an exocyclic haloalkyliene via direct halocyclization between propargylamines, heterocumulenes and I_2 (NBS). Tetrahedron 2015;71(24):4219–26.

[8] Petersen R, Cohrt AE, Petersen MA, Wu P, Clausen MH, Nielsen TE. Synthesis of hexahydropyrrolo[2,1-a]isoquinoline compound libraries through a Pictet-Spengler cyclization/metal-catalyzed cross coupling/amidation sequence. Bioorg Med Chem 2015;23(11):2646–9.

[9] Murali A, Medda F, Winkler M, Giordanetto F, Kumar K. Branching cascades provide access to two amino-oxazoline compound libraries. Bioorg Med Chem 2015;23(11):2656–65.

[10] Sankar MG, Mantilli L, Bull J, Giordanetto F, Bauer JO, Strohmann C, et al. Stereoselective synthesis of a natural product inspired tetrahydroindolo[2,3-a]-quinolizine compound library. Bioorg Med Chem 2015;23(11):2614–20.

[11] Craven P, Aimon A, Dow M, Fleury-Bregeot N, Guilleux R, Morgentin R, et al. Design, synthesis and decoration of molecular scaolds for exploitation in the production of alkaloid-like libraries. Bioorg Med Chem 2015;23(11): 2629–35.

[12] Nortclie A, Moody CJ. Seven-membered ring scaolds for drug discovery: access to functionalised azepanes and oxepanes through diazocarbonyl chemistry. Bioorg Med Chem 2015;23(11):2730–5.

[13] Nickel S, Nickel P, Hellmert M, Ernst S, Jewell R, Pearce CA, et al. Synthesis of a hexahydropyrrolo indole (HPI) compound library. Bioorg Med Chem 2015;23(11):2636–45.

[14] van der Pijl F, van Delft FL, Rutjes FPJT. Synthesis and functionalization of bicyclic N,O-aceta;scaolds from furfural. Bioorg Med Chem 2015;23(11):2721–9.

[15] Frei MS, Bilyard MK, Alanine TA, Galloway WRJD, Stokes JE, Spring DR. Studies towards the synthesis of indolizin-5(3*H*)-one derivatives and related 6,5-azabicyclic scaolds by ring-closing metathesis. Bioorg Med Chem 2015;23(11): 2666–79.

[16] Storr TE, Cully SJ, Rawling MJ, Lewis W, Hamza D, Jones G, et al. Combining two-directional synthesis and tandem reactions. Part 21: exploitation of a dimeric macrocycle for chain terminus dierentiation and synthesis of an sp^3-rich library. Bioorg Med Chem 2015;23(11):2621–8.

[17] Colomer I, Adeniji O, Burslem GM, Craven P, Rasmussen MO, Willaume A, et al. Aminomethylhydroxylation of alkenes: exploitation in the synthesis of scaolds for small molecule libraries. Bioorg Med Chem 2015;23(11):2736–40.

[18] Patil P, Khoury K, Herdtweck E, Dömling A. MCR synthesis of a tetracyclic tetrazole scaold. Bioorg Med Chem 2015;23(11):2699–715.

[19] Padwal JD, Filippov DV, Narhe BD, Aertssen S, Beuving RJ, Benningshof JCJ, et al. Cyclopentitol as a scaold for a natural product-like compound library for drug discovery. Bioorg Med Chem 2015;23(11):2650–5.

[20] Petersen MA, Mortensen MA, Cohrt AE, Petersen R, Wu P, Fleury-Brégeot N, et al. Synthesis of 1,4,5 trisubstituted γ-lactams via a 3-component cascade reaction. Bioorg Med Chem 2015;23(11):2695–8.

[21] Kamal A, Babu KS, Hussaini SMA, Mahesh R, Alarifi A. Amberlite IR-120H, an efficient and recyclable solid phase catalyst for the synthesis of quinoxalines: a greener approach. Tetrahedron Lett 2015;56(21):2803–8.

[22] Shimoda Y, Yamamoto H. Silica gel-supported Brønsted acid: reactions in the column system. Tetrahedron Lett 2015;56(23):3090–2.

[23] Harmand TJ, Kulkarni SS, Bode JW. Optimized synthesis of a cyanosulfurylide linker for Fmoc-SPPS of C-terminal peptide α-ketoacids. Tetrahedron Lett 2015;56(23):3477–80.

[24] Ortega R, Sanchez-Quesada J, Lorenz C, Dolega G, Karawajczyk A, Sanz M, et al. Design and synthesis of 1,1-disubstituted-1-silacycloalkane-based compound libraries. Bioorg Med Chem 2015;23(11):2716–20.

[25] Moylan C, Sweed AMK, Shaker YM, Scanlan EM, Senge MO. Lead structures for applications in photodynamic therapy 7. Efficient synthesis of amphiphilic glycosylated lipid porphyrin derivatives: refining linker conjugation for potential PDT applications. Tetrahedron 2015;71(24):4145–53.

[26] Řezníčková E, Popa A, Gucký T, Zatloukal M, Havlíček L, Bazgier V, et al. 2,6,9-Trisubstituted purines as CRK3 kinase inhibitors with antileishmanial activity in vitro. Bioorg Med Chem Lett 2015;25(11):2298–301.

[27] Chinnababu B, Reddy SP, Rao PS, Reddy VL, Kumar BS, Rao JV, et al. Isolation, semi-synthesis and bio-evaluation of spatane derivatives from the brown algae *Stoechospermum marginatum*. Bioorg Med Chem Lett 2015;25(12):2479–83.

Further reading

Papers with relevance to combinatorial chemistry or solid-phase synthesis from other journals

Aouali M, Mhalla D, Allouche F, El Kaim L, Tounsi S, Trigui M, et al. Synthesis, antimicrobial and antioxidant activities of imidazotriazoles and new multicomponent reaction toward 5-amino-1-phenyl[1,2,4]triazole derivatives. Med Chem Res 2015;24(6):2732–41.

Bogolubsky AV, Moroz YS, Mykhailiuk PK, Ostapchuk EN, Rudnichenko AV, Dmytriv YV, et al. A one-pot parallel synthesis of alkyl sulfides, sulfoxides, and sulfones. ACS Comb Sci 2015;17(6):348–54.

Dufour-Gallant J, Chatenet D, Lubell WD. De Novo Conception of Small Molecule Modulators Based on Endogenous Peptide Ligands: Pyrrolodiazepin-2-one γ-Turn Mimics That Dierentially Modulate Urotensin II Receptor-Mediated Vasoconstriction ex Vivo. J Med Chem 2015;58(11):4624–37.

Fridkin G, Columbus I, Saphier S, Yehezkel L, Goldvaser M, Marciano D, et al. Component Mobility by a Minute Quantity of the Appropriate Solvent as a Principal Motif in the Acceleration of Solid-Supported Reactions. J Org Chem 2015;80(10):5176–88.

Fueloepova V, Funk P, Popa I, McMaster C, Soural M. Solid-phase synthesis of trisubstituted benzo[f][1,2,3]triazolo[1,5-a][1,4]diazepin-6(5H)-ones and their sulfonyl analogues under mild reaction conditions. Eur J Org Chem 2015; 2015(16):3551–7.

Galibert M, Piller V, Piller F, Aucagne V, Delmas AF. Combining triazole ligation and enzymatic glycosylation on solid phase simplifies the synthesis of very long glycoprotein analogues. Chem Sci 2015;6:3617–23.

Hanashalshahaby EHA, Unaleroglu C. Mannich bases as enone precursors for water-mediated efficient synthesis of 2,3,6-trisubstituted pyridines and 5,6,7,8-tetrahydroquinolines. ACS Comb Sci 2015;17(6):374–80.

Hirai G, Sodeoka M. Focused library with a core structure extracted from natural products and modified: application to phosphatase inhibitors and several biochemical findings. Acc Chem Res 2015;48(5):1464–73.

Jiang L, Watkins D, Jin Y, Gong C, King A, Washington AZ, et al. Rapid synthesis, rna binding, and antibacterial screening of a peptidic-aminosugar (pa) library. ACS Chem Biol 2015;10(5):1278–9.

Jiang Q-Q, Sicking W, Ehlers M, Schmuck C. Discovery of potent inhibitors of human β-tryptase from pre-equilibrated dynamic combinatorial libraries. Chem Sci 2015;6(3):1792–800.

Kamalov M, Harris PWR, Wood JM, Brimble MA. On resin synthesis and cross-linking of collagen peptides containing the advanced glycation end-product pyrraline via Maillard condensation. Chem Commun (Cambridge, UK) 2015; 51(46):9475–8.

Kancherla R, Naveen T, Maiti D. Palladium-catalyzed [3+3] annulation between diarylamines and α, β-unsaturated acids through C–H activation: direct access to 4-substituted 2-quinolinones. Chem – Eur J 2015;21(23):8360–4.

Komnatnyy VV, Taveras KM, Nandurkar NS, Le Quement ST, Givskov M, Nielsen TE. Synthesis of substituted γ- and δ-lactams through mannich-type reactions of solid-supported n-acyliminium ions. Eur J Org Chem 2015;2015(16):3524–30.

Lai C-H, Hahm HS, Liang C-F, Seeberger PH. Automated solid-phase synthesis of oligosaccharides containing sialic acids. Beilstein J Org Chem 2015;11:617–21.

Lay M, Bannwarth W. Synthesis of 'head-to-tail' cyclized peptides on solid support using a chelating amide as new orthogonal protecting group. J Pept Sci 2015;21(6):461–6.

Lemrova B, Soural M. Synthetic strategies for preparing bicyclic guanidines. Eur J Org Chem 2015;2015(9):1869–86.

Malesevic M, Migge A, Hertel TC, Pietzsch M. A fluorescence-based array screen for transglutaminase substrates. ChemBioChem 2015;16(8):1169–74.

Mondal K, Pan SC. Copper(I)-catalyzed (z)-β-(tosyloxy)alkenyl iodide synthesis from (aryl)[(e)-β-(tosyloxy)alkenyl]iodonium tosylates: diversity-oriented synthesis of trisubstituted alkenes. Eur J Org Chem 2015;2015(10):2129–32.

Musumeci F, Schenone S, Desogus A, Nieddu E, Deodato D, Botta L. Click chemistry, a potent tool in medicinal sciences. Curr Med Chem 2015;22(17): 2022–50.

Ogasawara M, Wada S, Isshiki E, Kamimura T, Yanagisawa A, Takahashi T, et al. Enantioselective synthesis of planar-chiral ferrocene-fused 4-pyridones and their application in construction of pyridine-based organocatalyst library. Org Lett 2015;17(9):2286–9.

On-Resin Ugi Reactions. Application in the solid-phase synthesis of n-substituted and tetrazolo lipopeptides and peptidosteroids. Org Lett 2015;17(11):2728–31.

Pau A, Catto M, Pinna G, Frau S, Murineddu G, Asproni B, et al. Multitarget-directed tricyclic pyridazinones as g protein-coupled receptor ligands and cholinesterase inhibitors. ChemMedChem 2015;10(6):1054–70.

Rodriguez-Escrich C, Pericas MA. Organocatalysis on tap: enantioselective continuous flow processes mediated by solid-supported chiral organocatalysts. Eur J Org Chem 2015;2015(6):1173–88.

Seeberger PH. The logic of automated glycan assembly. Acc Chem Res 2015; 48(5):1450–63.

Shi Q, Kaiser TM, Dentmon ZW, Snyder JP, Ceruso M, Vullo D, et al. Design and validation of fresh, a drug discovery paradigm resting on robust chemical synthesis. ACS Med Chem Lett 2015;6(5):518–22.

Treder AP, Hickey JL, Tremblay M-CJ, Zaretsky S, Scully CCG, Mancuso J, et al. Solid-phase parallel synthesis of functionalised medium-to-large cyclic peptidomimet-

ics through three-component coupling driven by aziridine aldehyde dimers. Chem – Eur J 2015;21(25):9249–55.
Vanek V, Picha J, Fabre B, Budesinsky M, Lepsik M, Jiracek J. The development of a versatile trifunctional scaold for biological applications. Eur J Org Chem 2015;2015(17):3689–701.
Wales SM, Hammer KA, King AM, Tague AJ, Lyras D, Riley TV, et al. Binaphthyl-1,2,3-triazole peptidomimetics with activity against Clostridium difficile and other pathogenic bacteria. Org Biomol Chem 2015;13(20):5743–56.
Wang F-L, Guo Y, Li S-J, Guo Q-X, Shi J, Li Y-M. Diaminodiacid-based solid-phase synthesis of all-hydrocarbon stapled α-helical peptides. Org Biomol Chem 2015;13(22):6286–90.
Zhao Y-H, Ren X-F, Liu H-W. Synthesis of chiral benzofuran-derived β-amino esters induced by n-tert-butanesulfinamide. Synth Commun 2015;45(13): 1566–73.